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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,313	06/03/2002	Michael Hallek	50125/044001	5985

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 03/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,313	HALLEK ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *88,90,91 and 94-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *88,90,91 and 94-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/30/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed December 30, 2005 is acknowledged and entered. Claims 88, 90, 91, and 94-98 are pending and under examination.

2. The rejection of claims 74, 77-80 and 82-93 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is moot with regard to cancelled claims 74, 77-80, 82-87, 89, 92 and 93, and withdrawn with regard to amended claims 88, 90 and 91.

Claim Rejections - 35 USC § 112

3. Claims 88, 90, 91 and 94-98 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a method of reducing the antigenicity of an AAV particle, wherein the modifications to the VP1-3 include a large genus of modifications. In some embodiments, the deletion(s) is positioned between the BsrBI/HindII cleavage sites of the VP1-encoding nucleic acid. In other embodiments, the insertion occurs at a particular place along the VP3 protein. The claims encompass deletions and insertions at various points in the VP1 and VP3 regions. The claims also encompass deletions, insertions, replacements and substitutions anywhere along the VP1, VP2 and VP3 proteins. The particular type of deletion, insertion, etc.

is not specified in the claims. Applicant has not adequately described the types of modifications such that the large genus is sufficiently provided for.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the factors present in the claims are a partial structure to which the modification is made, and a functional result: reduced antigenicity, particle formation ability and infectivity. There is no identification of any particular portion of the VP1-3 structure that must be conserved when making the modifications such that only reduced antigenicity is achieved or particle formation and infectivity retained.

The specification provides one example of an insertion mutation into VP1 (see Example 1). The specification teaches that the insertion mutation of Example 1 was carried out at defined sites in the plasmid (see Example 1) by means of the PCR-assisted mutagenesis known to the skilled worker. According to Applicant's teachings, one of skill in the art would be able to use PCR-assisted mutagenesis to discover other modifications that may be made to the structural proteins VPs 1-3. The Office does not consider further discovery and experimentation to be adequate description for the large genus of modifications claimed.

Applicant's arguments have been carefully considered but fail to persuade. Applicant argues that the claims as amended specify particular sites within the AAV structural proteins that are modified and further specify what type of modification is to be made.

In response to Applicant's arguments, although Applicant has specified a general region where to make the modification (VPs 1-3) and what the end result should be (functional characteristics like reduced antigenicity), the large genus is not adequately defined by a structure/function correlation. Specifically, the modification has not be correlated to the disclosed function. One of skill in the art would have to experiment to find out which types of modifications result in reduced antigenicity. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Claim Rejections - 35 USC § 102

4. Claims 88, 90, 91 and 94-98 are rejected under 35 U.S.C. 102(b) as being anticipated by Mamounas *et al.* (WO 97/38723, herein, "Mamounas"). The claims as amended are drawn to a method for reducing the antigenicity of AAV comprising modifying AAV VP1, VP2 or VP3 in such a way as to bring about reduction in the antigenicity of AAV virus, and maintain particle formation and infectivity. Specifically, at least one of the modifications is based on a covalent or non-covalent linkage to the structural protein of one or more components listed in claims 94-97.

The teachings of Mamounas are reiterated for convenience. Mamounas discloses a capsid protein (structural protein) of AAV-2 that has been deleted (modified) in the VP1 or VP3 region (Example 1, pages 60-61, bridging paragraph, and page 67, part C). The deletion results in reduced specificity of the virus for the AAV receptor (page 4, lines 22-26), which is a reduction of the antigenicity of the virus for its natural receptor. Mamounas modifications of the VP1, VP2 and VP3 genes include the end of the AAV capsid gene open reading frame, and the

start codon of the individual capsid genes (page 67, lines 13-22). Anti-CD34 scFv sequence was ligated to the 5' end of the VP1, VP2, and VP3 sequences using HindIII and NotI sites (page 67, lines 21-26), thus qualifying as a further modification in addition to the deletion(s) in the VP 1 and/or VP3 region. Some of the insertions occur in the XhoI and XbaI cleavage sites (page 67, lines 21-23). Mamounas also teaches deleting a region of the VP1 or VP3 region and inserting a targeting ligand, which is an additional modification (page 4, lines 28-31). Antibodies, such as single chain variable region fragments, biotin, poly-L-lysine, transferrin, and other proteins are contemplated by Mamounas for integration into the VP regions (pages 30-32). Mamounas does not explicitly say that the insertion occurs between the BsrBI/HindII cleavage sites of the VP-1 encoding nucleic acid, however, since insertions occurred in the XhoI cleavage site, the insertions would be expected to take place somewhere within the BsrBI/HindII cleavage site because BsrBI/HindII cleavage sites are within the XhoI cleavage site. Regarding claim 91, which has the limitation of specific locations of insertions in VP3, the claims only require that the insertion be located before and/or after at least one amino acid in a sequence. Given that the claims only require that the insertion be before or after an amino acid, one would expect that the insertions by Mamounas would have occurred before or after an amino acid. Therefore, the claims are anticipated by Mamounas.

Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant argues that Mamounas fails to disclose the claimed invention, specifically, a method for reducing the antigenicity of AAV. Applicant argues that Mamounas' AAV vector's structural protein is incapable of supporting viral particle formation.

Applicant argues that the present claims require that it is the "modified structural protein" that "forms AAV particles", and that "the AAV having the modified structural protein retains infectivity". Applicant argues that the term "comprising" elsewhere in the claims does not change or negate the requirement.

- In response to Applicant's arguments, Mamounas's VP1 protein is modified. While Mamounas had to use a triple plasmid strategy to get intact viral particles, one cannot conclude that the modified VP1 protein did not retain infectivity. VP1 is just part of the capsid protein. Since Mamounas' VP1 portion of the capsid protein was modified, the entire capsid protein (combined with VP2 and VP3) qualifies as a modified structural protein that forms AAV particles. One would expect the particles to retain infectivity since the Mamounas' AAV vectors are targeted to cells, and thus have to have infectivity capabilities. Further, the claims recite, "wherein the modification brings about a reduction in the antigenicity of the virus". Therefore, the reduced antigencity relates to the virus as a whole, not just one protein.

- Applicant argues that the following statement from the Office is incorrect: "The deletion [of Mamounas] results in reduced specificity of the virus for the AAV receptor (page 4, lines 22-26), which is a reduction in the antigenicity of the virus for its natural receptor". Applicant argues that reduction in antigenicity refers to reduction in a host antibody response or antibody binding interaction with the AAV particle, and not to the interaction of the virus with its receptor.

- In response to Applicant's argument, the Office maintains its position that Mamounas' modified capsid protein would reduce antigenicity. One would expect that modifying the epitopes of the capsid protein would ultimately result in a lowered antibody response to the AAV. The existing antibodies circulating in the host would not recognize the portion of the capsid protein that was modified by Mamounas. When the Office stated that the interaction of the virus with its receptor is reduced, antibody paratopes were meant to be encompassed by the term, "receptor". The Office regrets any confusion over the terminology used.

- Applicant argues that with respect to the XhoI and XbaI insertions, the Office has mischaracterized the Mamounas reference as teaching the claimed invention. In particular, Applicant argues that the claims as amended do not include an XbaI insertion. Applicant also argues that the XhoI site referred to by Mamounas is not an insertion site in the AAV sequence, but rather a cloning site.
  - In response to this argument, the Office recognizes that the claims no longer recite insertions in the XhoI and XbaI cleavage sites.
- Applicant argues that the Mamounas deletions referred to by the Office do not occur at the same sites as the deletions and insertions presently claimed. Mamounas' deletions are summarized in Table 1, page 61 and 62. The deletions occur in after nucleotides 2278, while Applicant's deletions occur after nucleotide 2971.
  - In response to Applicant's argument, claim 91 is the only claim that specifies the location of the insertion with regard to specific amino acids. Note that the claim reads, "wherein the modification(s) is/are one or more insertions that is/are

located adjacent to at least one amino acid in a sequence selected from the group consisting of" SEQ ID NO: 2-9. The claim reads on an insertion at any place adjacent to a Y, K, Q, I, S, A, etc. In other words, the claims do not specify enough where the insertion takes place such that Mamounas's insertion does not read on the claimed insertion. Therefore, the rejection is maintained as anticipated by Mamounas' AAV viral particle having a modified VP1.

Conclusion

5. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

SBC

Stacy B. Chen
March 10, 2006

James C. Housel 3/19/06

JAMES HOUSEL
SUPERVISORY PATENT EXAMINER
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